

# Effects of feed intake restriction during late pregnancy on maternal metabolic changes and fetal development in ewes

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**ABSTRACT:** This study investigated the effects of feed intake restriction during late pregnancy on maternal metabolic changes and fetal development in ewes. Six ewes out of 35 Mongolian ewes were slaughtered at the beginning of the experiment and the remaining 29 animals were allocated to three different groups: Restricted Group 1 (RG1; 0.175 MJME BW<sup>-0.75</sup>/day,  $n = 12$ ), Restricted Group 2 (RG2; 0.33 MJME BW<sup>-0.75</sup>/day,  $n = 9$ ), and Control Group (CG; *ad libitum*, 0.67 MJME BW<sup>-0.75</sup>/day,  $n = 8$ ). At 140 days (d) of gestation, 6 representative ewes from each group were slaughtered. The results indicated the maternal net body weight loss, the concentrations of glucose (GLU) (120 d), GLU (140 d), total amino acid (TAA) (140 d), total protein (TP) (140 d), albumin (ALB) (140 d), and globulin (GLB) (140 d) were significantly ( $P < 0.01$ ) decreased, while those of nonesterified fatty acid (NEFA) (120 d), NEFA (140 d),  $\beta$ -hydroxybutyric acid (BHBA) (120 d), and BHBA (140 d) in maternal plasma were greatly enhanced in RG1 group compared to CG group ( $P < 0.01$ ). For RG2 group, a significant decrease of the maternal net body weight loss ( $P < 0.01$ ) and the concentrations of GLU (140 d) ( $P < 0.01$ ), TAA (140 d) ( $P < 0.01$ ), ALB (140 d) ( $P < 0.01$ ), GLB (140 d) ( $P < 0.05$ ), and a significant increase of NEFA (120 d) ( $P < 0.05$ ) and NEFA (140 d) ( $P < 0.01$ ) in maternal plasma were found in relation to CG group. Furthermore, the fetal weight was significantly reduced in RG1 and RG2 groups ( $P < 0.01$ ), and body length ( $P < 0.05$ ), thoracic girth ( $P < 0.05$ ), thoracic depth ( $P < 0.05$ ), abdomen circumference ( $P < 0.05$ ), straighted crown-rump length ( $P < 0.01$ ), and curved crown-rump length ( $P < 0.01$ ) in RG1 group were also decreased compared to CG group. With the decrease of nutrient level during late pregnancy, the maternal protective buffer system in RG2 group still played a major role, but the system in RG1 group might have been destroyed, which resulted in serious impacts on the fetal growth and development.

**Keywords:** Mongolian ewes; nutrition level; late gestation; physiological metabolism; fetal growth

**List of abbreviations:** GLU = glucose, TAA = total amino acid, TP = total protein, ALB = albumin, GLB = globulin, NEFA = nonesterified fatty acid, BHBA =  $\beta$ -hydroxybutyric acid, INBW = initial net body weight, FNBW = final net body weight, NBWL = net body weight loss

## INTRODUCTION

Adaptation of ewes to undernutrition may alter synthesis of nutrients and physiological metabolism (Reynolds et al. 2006). Maternal undernutrition

during pregnancy retarding the fetal growth and development (Redmer et al. 2004), known as intrauterine growth restriction (IUGR), may lead to permanent alterations of physiological processes in the offspring (Robinson et al. 1999; Wu et al.

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2006; Langley-Evans et al. 2010; Hanson et al. 2011) and may be associated with an increased risk of perinatal morbidity and mortality (McMillen et al. 2001; Gao et al. 2007). According to the degree of “protective buffer system”, the maternal body is able to adaptively regulate the physiological metabolism of carbohydrates, protein, and fat by endocrine system to provide nutrients for fetal development (Gluckman et al. 2005; Gao et al. 2007). But the alternations of maternal metabolic status regulated by endocrine would affect the fetal growth to different extent, and with the supply of nutrition continuously decreasing, the protective buffer system of maternal body would be challenged (Gao et al. 2007).

As one of the major complications of perinatal period, IUGR could not only result in perturbations to fetal development (Louey et al. 2000; Micke et al. 2010) and alter the ontogeny of fetal organ growth and development (Gao et al. 2009), but also might be the reason of a number of diseases in later life, including insulin resistance (Ye et al. 2012), high blood pressure (Gluckman and Hanson 2004; Ingelfinger and Nuyt 2012), coronary artery disease (Barker 1999; Visentin et al. 2013), and respiratory diseases (Maritz et al. 2004). Maternal “protective buffer system” is the powerful protection of fetal growth, and fully comprehending the effects of physiological metabolic changes on ewes and on the degree of fetal development during late pregnancy is a theoretical basis for further study of IUGR. Despite the significant effects on clinical and agricultural domains, the mechanism by which feed intake restriction during late pregnancy affects maternal metabolic changes and fetal development, remains unknown. Therefore, focusing our attention on maternal environment can elucidate the consequences of fetal growth retardation and help better understanding the postnatal growth. Thus, the objective of this study was to investigate the effects of feed intake restriction during late pregnancy on maternal metabolic changes and fetal development.

## MATERIAL AND METHODS

**Animals and treatments.** Thirty-five Mongolian ewes with singleton fetuses in their second or third parity, which had similar live weights (mean  $52.93 \pm 2.62$  kg) were mated at a synchronized oestrus. Based on the fact that the fetus is considered to achieve 80–85% of its final birth weight during the last two months of pregnancy (Robinson et al. 1999; Symonds et al. 2001), maternal undernutrition was carried out from day 90 till day 140 of gestation. At day 90 of pregnancy, 6 ewes were slaughtered at the beginning of the experiment and the remaining 29 animals were allocated to three different groups (Table 1): Restricted Group 1 (RG1;  $0.175 \text{ MJME BW}^{-0.75}/\text{day}$ ,  $n = 12$ ), Restricted Group 2 (RG2;  $0.33 \text{ MJME BW}^{-0.75}/\text{day}$ ,  $n = 9$ ), and Control Group (CG; *ad libitum*,  $0.67 \text{ MJME BW}^{-0.75}/\text{day}$ ,  $n = 8$ ). At 140 days of pregnancy, six representative ewes in each group were slaughtered and fetal body weight, body length, thoracic girth, thoracic depth, abdomen circumference, straightened crown-rump length, and curved crown-rump length were measured respectively.

**Feeding and management.** All animals were housed in individual pens and fed chopped natural hay (Table 2). Following a one-week acclimatization, the amount of feed offered was constant throughout the restricted period. Restricted ewes were fed at 8:30 and 16:00 h each day. The ewes in control group were offered feed at 8:30, 11:00, and 16:00 h daily (the feed refusals were approximately 10% of the total amount offered). The animals had free access to water and mineral mixture block. The feed refusals were collected daily and recorded before feeding at 8:30 h and sub-sampled for chemical analysis.

**Body weight and maternal net body weight loss.** At the beginning of the experiment (day 90 of gestation), the weights of the conceptus constituents in the ewes (including the weights of fetus,

Table 1. Chemical composition and nutritive value (DM) of grass fed and left during restriction period (late pregnancy)

	Nutrients composition								
	ME (MJ/kg)	DM (%)	CP (%)	EE (%)	NDF (%)	ADF (%)	ASH (%)	Ca (%)	P (%)
Fed grass	8.90	88.42	10.09	4.34	71.98	35.82	4.67	0.57	0.09
Left grass	–	92.04	9.27	2.72	71.19	36.60	4.39	0.68	0.08

ME = metabolizable energy, DM = dry matter, CP = crude protein, EE = ether extract, NDF = neutral detergent fibre, ADF = acid detergent fibre

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Table 2. Maternal nutrition in experimental groups during restriction period (late pregnancy)

Groups	CG ( <i>n</i> = 10)	RG2 ( <i>n</i> = 11)	RG1 ( <i>n</i> = 14)
Daily ME intake (MJ/BW <sup>-0.75</sup> /day)	0.670	0.330	0.175
Mean daily grass intake (g/day)	1689.05	842.49	440.18
Mean daily crude protein intake (g/day)	170.43	85.01	44.41

CG = control group, *ad libitum* (0.67 MJME BW<sup>-0.75</sup>/day), RG1 = Restricted Group 1 (0.175 MJME BW<sup>-0.75</sup>/day), RG2 = Restricted Group 2 (0.33 MJME BW<sup>-0.75</sup>/day), ME = metabolizable energy, BW = body weight

placenta, and amniotic fluid) subtracted from maternal body weight gave maternal initial net body weight (INBW). At the end of the experiment (day 140 of gestation), the body weight of ewe with removed placenta was the final net body weight (FNBW). INBW subtracted by FNBW gave the maternal net body weight loss during restriction (NBWL).

**Sampling blood and assays of GLU, NEFA, TAA, BHBA, TP, and ALB concentrations in maternal plasma.** Jugular blood samples (10 ml) were taken on days 90, 120, and 140 of gestation in each group. The blood was collected into heparinized tubes and centrifuged (3500 *g*, 15 min) and the plasma was stored at –70°C. Commercial kits were purchased to determine the glucose (GLU) (050520, Prodia Diagnostics, Botzingen, Germany), nonesterified fatty acid (NEFA) (095207, Hydrops Medical Corp., Tokyo, Japan), total amino acid (TAA) (A026, NanJing Jiancheng Biological Corp., NanJing, China), β-hydroxybutyric acid (BHBA) (BHB0210, Shanghai Jingyuan medical apparatus and instruments Corp., Shanghai, China), total protein (TP) (20110422, Kehua Biological Corp., Shanghai, China), and albumin (ALB) (20110622, Kehua Biological Corp.) concentrations in mater-

nal plasma using a Hitachi automatic biochemical analyzer 7600-020 (Hitachi, Tokyo, Japan).

**Statistical analysis.** All the data were assessed using the ANOVA procedure of the SAS software (Statistical Analysis System, Version 8.01, 2001). The model was as follows:

$$Y_i = \mu + M_i + e_i$$

where:

$\mu$  = overall mean

$M_i$  = fixed effect of the nutrition treatments ( $i = 1-3$ )

$e_i$  = random residual error

Duncan's Multiple Range Test was used to identify significant differences between mean values. Significance was declared at  $P < 0.05$  and  $P < 0.01$ .

## RESULTS

**Maternal net body loss.** There was no significant difference in maternal initial net body weight ( $P > 0.05$ ) on day 90 of gestation (Table 3). With the decreasing of the dietary energy density, maternal final net body weight in RG1 group was significantly reduced compared with RG2 ( $P < 0.05$ ) and CG groups ( $P < 0.01$ ). Maternal net body weight lost was 7.24 kg, 11.41 kg, and mobilized 14.24%,

Table 3. Effects of maternal undernutrition during late pregnancy on maternal net body weight loss (kg) (values are means ± SEM)

Groups	CG ( <i>n</i> = 6)	RG2 ( <i>n</i> = 6)	RG1 ( <i>n</i> = 6)	SEM	<i>P</i> -value <sup>1</sup>
INBW	50.92 <sup>a</sup>	50.97 <sup>a</sup>	50.39 <sup>a</sup>	0.82	1.2415
FNBW	52.62 <sup>a</sup>	43.85 <sup>c</sup>	38.67 <sup>d</sup>	1.37	0.0001
NBWL	2.76 <sup>a</sup>	–7.24 <sup>c</sup>	–11.41 <sup>e</sup>	0.40	0.0001
NBWL/INBW × 100 (%)	5.63 <sup>a</sup>	–14.24 <sup>c</sup>	–22.91 <sup>e</sup>	0.01	0.0001

CG = control group (*ad libitum*, 0.67 MJME BW<sup>-0.75</sup>/day), RG1 = Restricted Group 1 (0.175 MJME BW<sup>-0.75</sup>/day), RG2 = Restricted Group 2 (0.33 MJME BW<sup>-0.75</sup>/day), INBW = initial net body weight, NBWL = net body weight loss, FNBW = final net body weight

<sup>a-e</sup>identical letters within a row mean no significant difference ( $P > 0.05$ ), adjacent superscripts mean significant difference ( $P < 0.05$ ), and interval superscripts mean a very significant difference ( $P < 0.01$ )

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Table 4. Effects of maternal undernutrition during late pregnancy on the concentration changes of GLU, NEFA, TAA, BHBA, TP, ALB, GLB, ALB/GLB in maternal plasma (days 90, 120, and 140 of gestation;  $n = 6$  per each group; values are means  $\pm$  SEM)

Items	Day 90	Day 120			SEM	P-value <sup>1</sup>	Day 140			SEM	P-value <sup>1</sup>
		CG	RG2	RG1			CG	RG2	RG1		
GLU (mmol/l)	3.24	3.56 <sup>a</sup>	3.09 <sup>a</sup>	1.97 <sup>c</sup>	0.1594	0.0002	3.46 <sup>a</sup>	2.45 <sup>c</sup>	1.54 <sup>e</sup>	0.12	0.0001
NEFA ( $\mu$ Eq/l)	87.50	178.5 <sup>c</sup>	931.67 <sup>b</sup>	1479.50 <sup>a</sup>	118.64	0.0002	415.75 <sup>c</sup>	1186.5 <sup>a</sup>	1236.80 <sup>a</sup>	57.93	0.0001
TAA ( $\mu$ mol/l)	4.17	3.50 <sup>a</sup>	3.55 <sup>a</sup>	2.84 <sup>a</sup>	0.5569	0.6533	9.11 <sup>a</sup>	4.32 <sup>c</sup>	1.08 <sup>e</sup>	0.52	0.0001
BHBA (mmol/l)	0.40	0.36 <sup>c</sup>	0.48 <sup>c</sup>	2.49 <sup>a</sup>	0.1581	0.0001	0.53 <sup>c</sup>	0.76 <sup>c</sup>	2.61 <sup>a</sup>	0.15	0.0001
TP (g/l)	66.70	71.58 <sup>a</sup>	65.55 <sup>a</sup>	64.90 <sup>a</sup>	2.2292	0.1187	68.58 <sup>a</sup>	63.84 <sup>ac</sup>	59.20 <sup>c</sup>	1.67	0.0065
ALB (g/l)	33.73	33.28 <sup>a</sup>	31.30 <sup>a</sup>	32.65 <sup>a</sup>	43.270	0.1767	32.86 <sup>a</sup>	30.18 <sup>c</sup>	30.00 <sup>c</sup>	0.48	0.0020
GLB (g/l)	32.98	38.30 <sup>a</sup>	37.33 <sup>a</sup>	32.25 <sup>a</sup>	1.9721	0.1309	35.72 <sup>a</sup>	32.30 <sup>b</sup>	27.55 <sup>c</sup>	1.01	0.0011
ALB/GLB	1.03	0.87 <sup>a</sup>	0.92 <sup>a</sup>	1.03 <sup>a</sup>	0.0791	0.4055	0.92 <sup>a</sup>	0.94 <sup>a</sup>	1.04 <sup>a</sup>	0.04	0.1738

GLU = glucose, TAA = total amino acid, TP = total protein, ALB = albumin, GLB = globulin, NEFA = nonesterified fatty acid, BHBA =  $\beta$ -hydroxybutyric acid, CG = control group (*ad libitum*, 0.67 MJME BW<sup>-0.75</sup>/day), RG1 = Restricted Group 1 (0.175 MJME BW<sup>-0.75</sup>/day), RG2 = Restricted Group 2 (0.33 MJME BW<sup>-0.75</sup>/day), BW = body weight

<sup>a–e</sup>identical letters within a row mean no significant difference ( $P > 0.05$ ), adjacent superscripts mean a significant difference ( $P < 0.05$ ), and interval superscripts mean a very significant difference ( $P < 0.01$ )

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22.91% of initial net body weight in RG2, RG1 groups, respectively ( $P < 0.01$ ).

**Maternal plasma parameters.** The concentration changes of GLU, NEFA, TAA, BHBA, TP, ALB, GLB, ALB/GLB in maternal plasma are compared in Table 4. On day 120 of gestation, the concentration of GLU in RG1 group was significantly lower than that in RG2 and CG groups ( $P < 0.01$ ), whereas the concentration of NEFA in RG1 ( $P < 0.01$ ) and RG2 ( $P < 0.05$ ) groups was increased when compared

to CG group, and the concentration of BHBA in RG1 group was greatly enhanced compared to RG2 and CG groups ( $P < 0.01$ ). On day 140 of gestation, a significant reduction of GLU, TAA, and ALB concentrations was found in restricted ewes ( $P < 0.01$ ). However, the concentration of NEFA in RG1 and RG2 groups was higher than that in CG group ( $P < 0.01$ ), and the concentration of BHBA in RG1 group was higher if compared to that in RG2 and CG groups ( $P < 0.01$ ). Moreover, a significant

Table 5. Effects of maternal undernutrition during late pregnancy on fetal weight and measurements ( $n = 6$  per each group; values are means  $\pm$  SEM)

Items	Day 90 of gestation	Day 140 of gestation			SEM	P-value <sup>1</sup>
		CG	RG2	RG1		
Weight (g)	523.98	3977.67 <sup>a</sup>	3572.60 <sup>c</sup>	3111.00 <sup>e</sup>	74.83	0.0001
Body length (cm)	16.07	29.84 <sup>a</sup>	28.68 <sup>ab</sup>	27.68 <sup>b</sup>	0.57	0.0700
Thoracic girth (cm)	16.47	32.38 <sup>a</sup>	31.60 <sup>ab</sup>	30.22 <sup>b</sup>	0.63	0.1100
Thoracic depth (cm)	7.15	14.08 <sup>a</sup>	13.45 <sup>ab</sup>	12.78 <sup>b</sup>	0.22	0.0041
Abdomen circumference (cm)	16.88	32.43 <sup>a</sup>	32.08 <sup>ab</sup>	31.03 <sup>b</sup>	0.36	0.0400
Straightened crown-rump length (cm)	24.10	44.53 <sup>a</sup>	43.87 <sup>ab</sup>	41.72 <sup>c</sup>	0.56	0.0079
Curved crown-rump length (cm)	30.18	53.72 <sup>a</sup>	51.78 <sup>ac</sup>	50.07 <sup>c</sup>	0.73	0.3200

CG = control group (*ad libitum*, 0.67 MJME BW<sup>-0.75</sup>/day), RG1 = Restricted Group 1 (0.175 MJME BW<sup>-0.75</sup>/day), RG2 = Restricted Group 2 (0.33 MJME BW<sup>-0.75</sup>/day), BW = body weight

<sup>a–e</sup>identical letters within a row mean no significant difference ( $P > 0.05$ ), adjacent superscripts mean a significant difference ( $P < 0.05$ ), interval superscripts mean a very significant difference ( $P < 0.01$ )

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decrease of TP concentration was observed in RG1 group in relation to CG group ( $P < 0.01$ ), and the concentration of GLB in RG1 ( $P < 0.01$ ) and RG2 ( $P < 0.05$ ) groups was reduced in comparison to that in CG group. The results indicated that, as pregnancy progressed, the metabolic responses of ewes were greatly and to different extent affected by the lower energy density.

**Fetal weight and body measurements.** The effects of maternal undernutrition during late pregnancy on fetal weight and body measurements are presented in Table 5. With the decreasing dietary energy density, the fetal body weight was significantly ( $P < 0.01$ ) reduced in RG1 and RG2 groups when compared to CG group. The values of fetal body length ( $P < 0.05$ ), thoracic girth ( $P < 0.05$ ), thoracic depth ( $P < 0.05$ ), abdomen circumference ( $P < 0.05$ ), straighted crown-rump length ( $P < 0.01$ ), and curved crown-rump length ( $P < 0.01$ ) in RG1 group were significantly lower than those of CG group. Although the fetal body length, thoracic girth, thoracic depth, abdomen circumference, straighted crown-rump length, and curved crown-rump length in RG2 group had the trend to decrease, there were no significant differences ( $P > 0.05$ ).

## DISCUSSION

In response to undernutrition, the animal body weight is lost rapidly during pregnancy (Chilliard et al. 1998). In the present study, in order to maintain pregnancy and ensure maximum fetal growth, the maternal body mobilized reserves to supply energy according to the degree of restriction and made adaptive regulations instinctively during the period of undernutrition, which led to the reduction of 14.24% and 22.91% of initial net body weight respectively in RG2 and RG1 groups ( $P < 0.01$ ).

The GLU concentration in plasma, which reflects absorption, metabolic homeostasis, and operation of GLU, is a performance of the body's energy metabolism level (Su et al. 2013). In the present study, the GLU concentration was reduced with the decreasing nutrition level, which is in agreement with the results of Lekatz et al. (2011). The data indicate that the GLU concentration in restricted groups trended to be lower with the reduction of nutrition level, and the ewes in RG2 group had a buffer range to adapt to early undernutrition environment. The lower GLU concentration in RG1

group affected the maternal energy balance, and at this point, in order to keep normal life activity, fatty acids became the major source of energy (Chilliard et al. 1998; Limesand et al. 2007), which led to the decrease of TAA concentration and the increase of BHBA and NEFA concentrations in RG1 group. The higher NEFA and BHBA concentrations are an important signal of the body on fat mobilization resulting in negative energy balance, ketosis, and fatty liver (Zhang and Tan 2007). Although the NEFA concentration was increased significantly, there were no differences in the HBA concentration in RG2 group, which indicated that the oxidation rate of BHBA was controllable in a certain range. However, the accumulation of BHBA and NEFA in the ewes of RG1 group led to a series of metabolic disorders. In addition, the changed TP, ALB, GLB, and ALB/GLB in plasma could reflect in the function of the liver, energy metabolism, and immune function status of animal body (Su et al. 2013). When liver function is compromised, the ability to synthesize protein is reduced, which also leads to the decreasing TP and ALB concentrations in plasma (Wang et al. 2004). In this study, the significant decrease of TP, ALB, and GLB concentrations in RG1 could have seriously impaired the liver function and lowered the synthesis capacity and efficiency of protein in ewes. However, there was no significant change in the TP concentrations between RG2 and CG groups. Perhaps the maternal protective buffer system in RG2 group played an important role in preventing the liver from harm. The different changed extent of metabolites in maternal plasma during late pregnancy might be the key factor for fetal development.

Perturbations in maternal nutrition during pregnancy may programme the permanent structure and physiological modification in fetal development (Symonds et al. 2001; Osgerby et al. 2002; Gao et al. 2007; Micke et al. 2010). In the current study, the fetal body weight was reduced ( $P < 0.01$ ) and the body length, thoracic girth, thoracic depth, abdomen circumference, straighted crown-rump length, and curved crown-rump length in RG1 group were significantly affected by maternal undernutrition during late pregnancy, which was in agreement with the results of Gao et al. (2009) and Regnault et al. (2007). Although the fetal weight in RG2 group was significantly decreased when compared to CG group ( $P < 0.01$ ), the body length, thoracic girth, thoracic depth, abdomen circumfer-

ence, straighted crown-rump length, and curved crown-rump length were not significantly different from those of CG group ( $P > 0.05$ ). The results on the fetal development indicated that with the decreasing nutrient level during late pregnancy, the maternal protective buffer system in RG2 group still played a major role, but the system in RG1 group might be destroyed, which resulted in serious impacts on fetal growth and development.

## CONCLUSION

In conclusion, the maternal physiological metabolism and fetal growth were significantly affected by the feed intake restriction and its different extent in ewes during late pregnancy might be the key factor for different growth trajectories in postnatal animals. These perturbations in fetal growth, in turn, may have significant implications on adult health, significantly raising health and economic issues both in medical and agricultural sectors.

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